Chapter 5 An acid functionalized helicene – The long and winding road

The decision to place a carboxylic acid group in a hexahelicene and how to do so

In this chapter, the synthesis of an acid functionalized hexahelicene is described together with synthetic considerations that led to the final choice of the target.

5.1 Introduction

As described in the previous chapter, the choice of position of the functional group might have led to poor crystal packing and this might have caused the aminohelicene not to be a conglomerate. Also we found that an amino-functionalized helicene was sensitive to oxidation. Storage in the cold under an inert atmosphere is necessary. Acetylation or salt formation should lead to a more stable derivative. Both for reason of stability, and the desire to have access to both a basic as well as an acidic helicene, we decided to introduce a carboxylic acid functional group, and chose a position more on the side of the helicene, namely the 7-position.

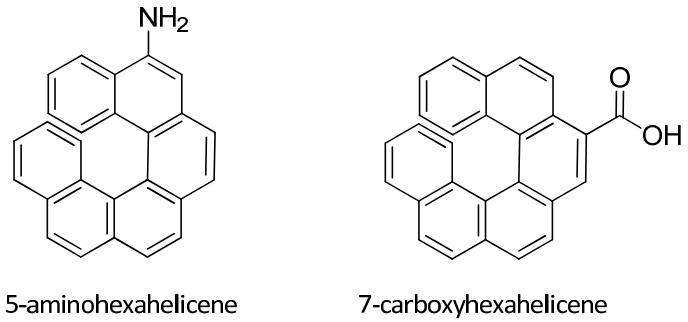


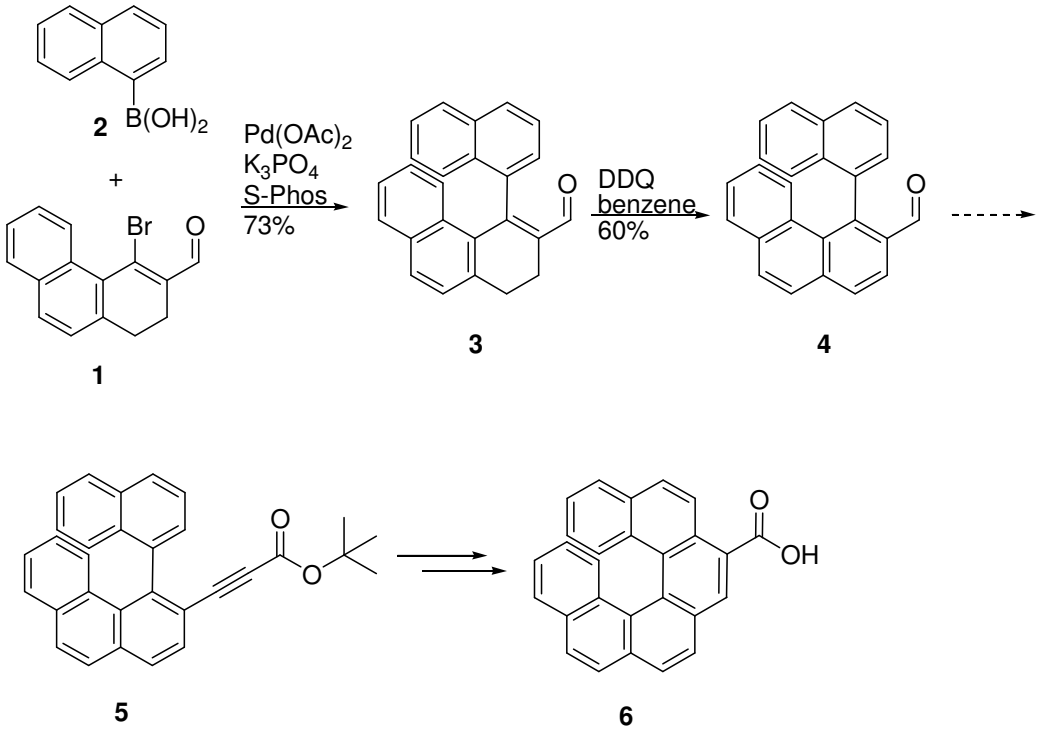
Figure 1: targeted functionalized helicenes

In contrast to 5-aminohexahelicene, this synthesis was not easy. The various routes followed are described, together with a discussion why certain approaches, although seemingly logical, failed at certain key points. The chapter closes with the description of the ultimately successful route to 7-carboxyhexahelicene and its behavior on surfaces.

5.2 Synthetic strategies towards 7-carboxyhexahelicene

5.2.1 Adapted aminohelicene route

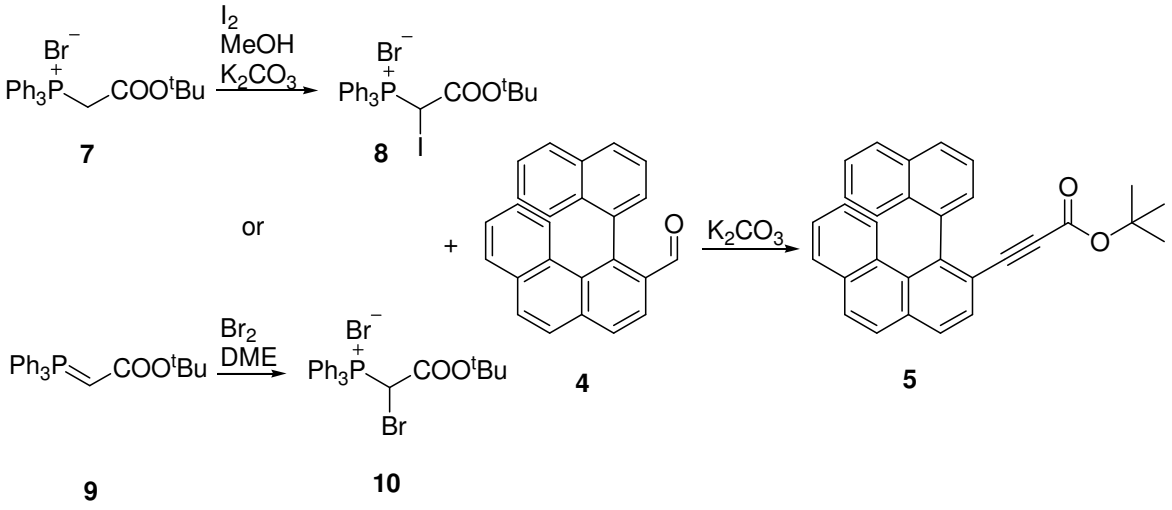
The first attempt to synthesize an acid functionalized helicene, summarized in scheme 1, was to use existing building block **1** as an available synthon in a route similar to that used for 5-aminohexahelicene:



*Scheme 1: Strategy for the synthesis of acid functionalized helicene **6**.*

Aldehyde **3** was prepared using the same conditions for the Suzuki reaction as for the amino-functionalized helicene. This gave **3** in 73% yield. DDQ oxidation gave aldehyde **4** in 60% yield.

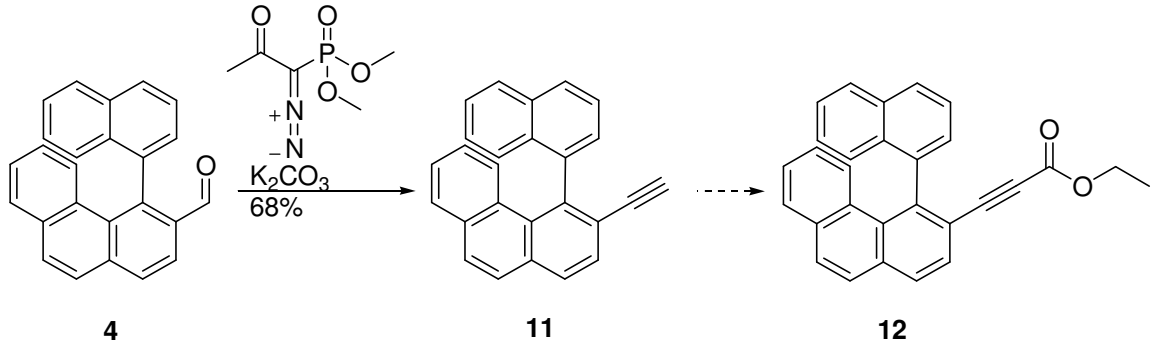
The next step was to convert the aldehyde to an acid functionalized alkyne. We first tested iodide **8** as reagent to introduce the propiolic acid moiety[1] via a Wittig reaction, as shown in scheme 2:



*Scheme 2: A Wittig-type strategy towards propiolic acid **5***

There were already some questions about the stability of iodide **8**, and indeed in the reaction with aldehyde **4**, no conversion was observed. Furthermore, the reaction with the more stable bromide **10**[2] also failed to give the desired compound.

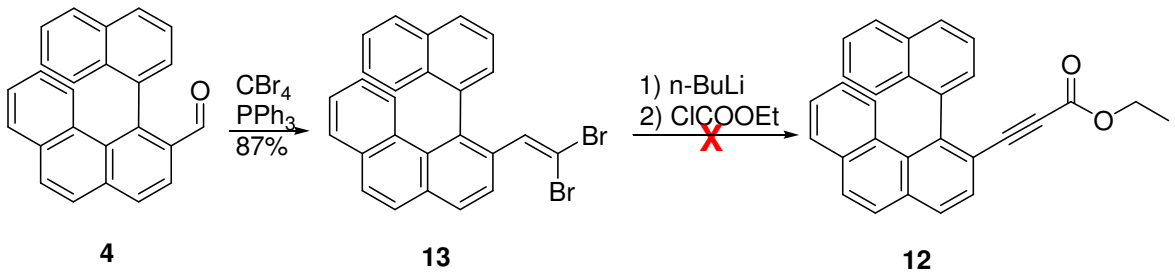
We then sought to introduce the unsubstituted alkyne functionality first, followed by carboxylation (scheme 3).



*Scheme 3: Strategy to prepare alkyn **11** and subsequent carboxylation*

Using the Ohira-Bestman reagent, aldehyde **4** could be converted to alkyne **11** in 68% yield. We then tried to functionalize the alkyne using ethyl chloroformate and DMAP, DIPEA and $Pd(Ph_3P)_4$[3] or with n-BuLi and ethyl chloroformate[4] but both attempts were unsuccessful.

The dibromoalkene approach, described by Fürstner *et al.*[5] (scheme 4), was examined to prepare alkyne **12**, as shown in scheme 4:

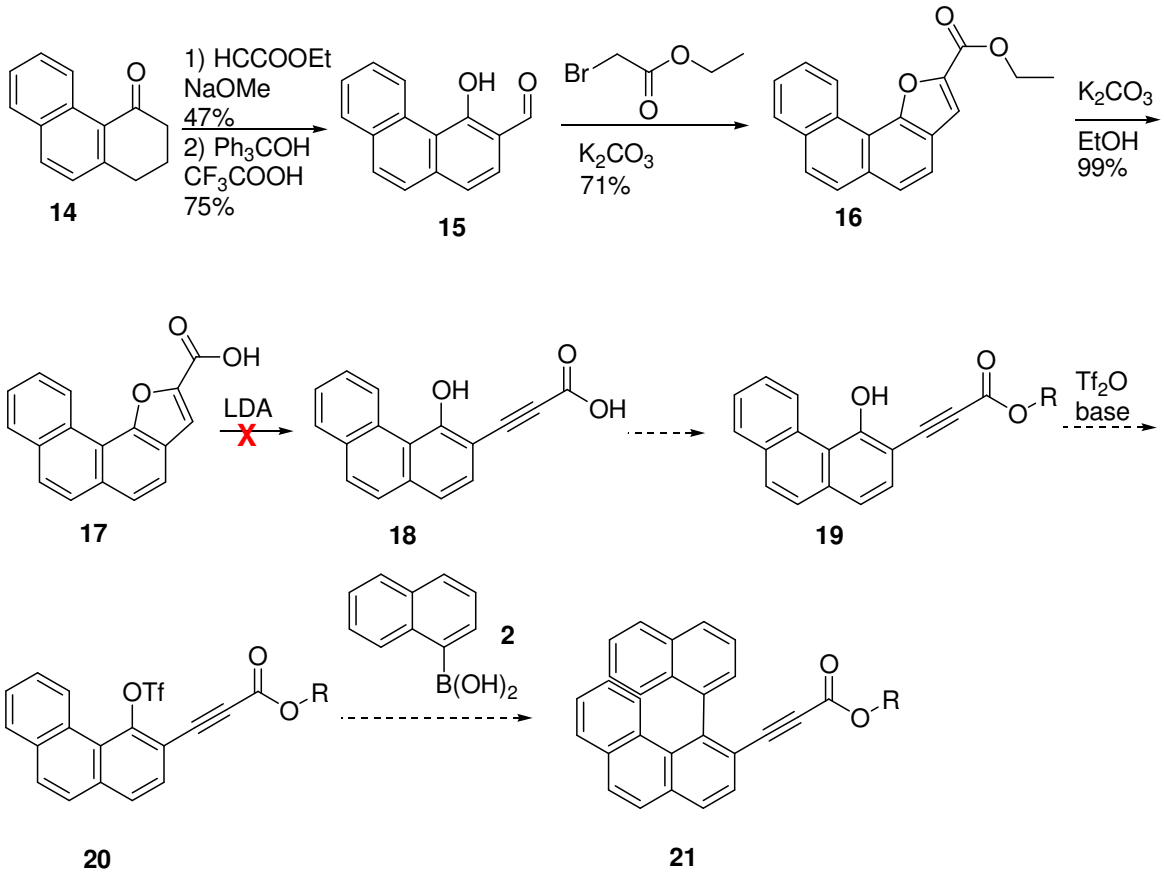


4 **13** **12**

*Scheme 4: Route to propiolic acid **12** via a dibromoalkene route*

The formation of dibromide **13** proceeded well, but attempts at further reaction with ethyl chloroformate led to the formation of unsubstituted alkyne **11** (the vinyl anion formed by bromo-lithium exchange probably collapses to a carbene that forms **11**, which as previously shown, is insensitive to carboxylation).

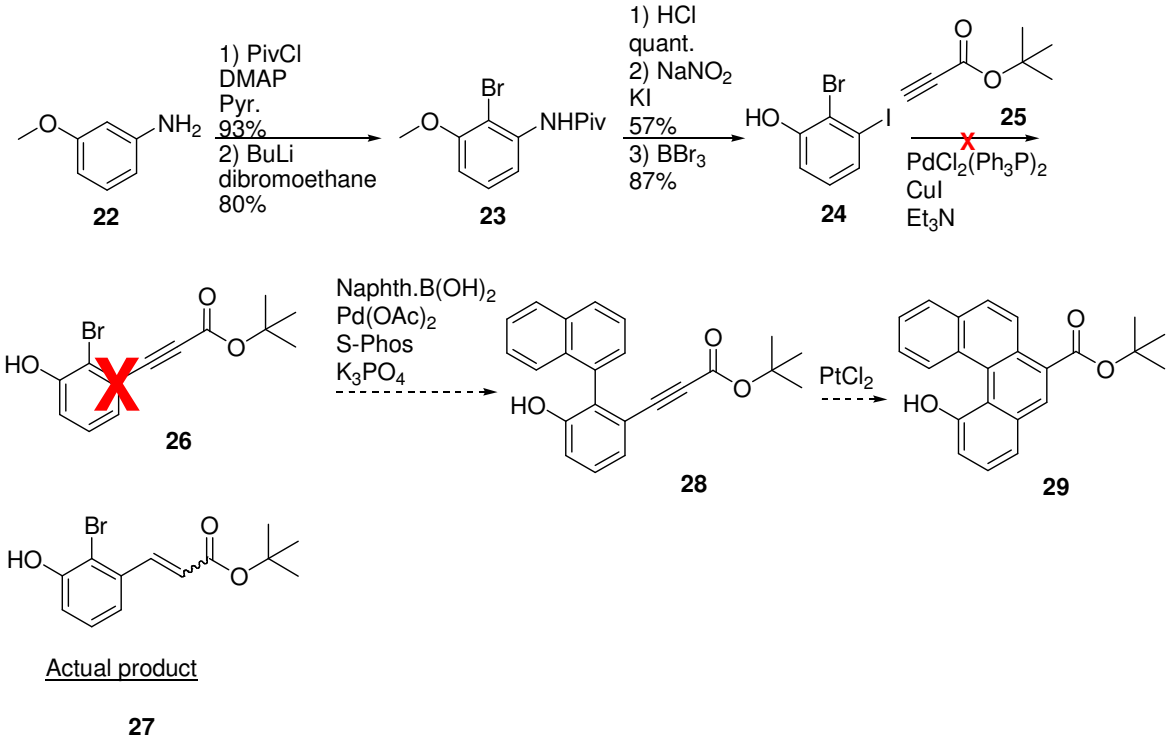
In an alternative approach, we sought to introduce first the propiolic acid functionality and then perform the Suzuki coupling. This strategy is shown in scheme 5:



Scheme 5: route using propiolic ester triflate

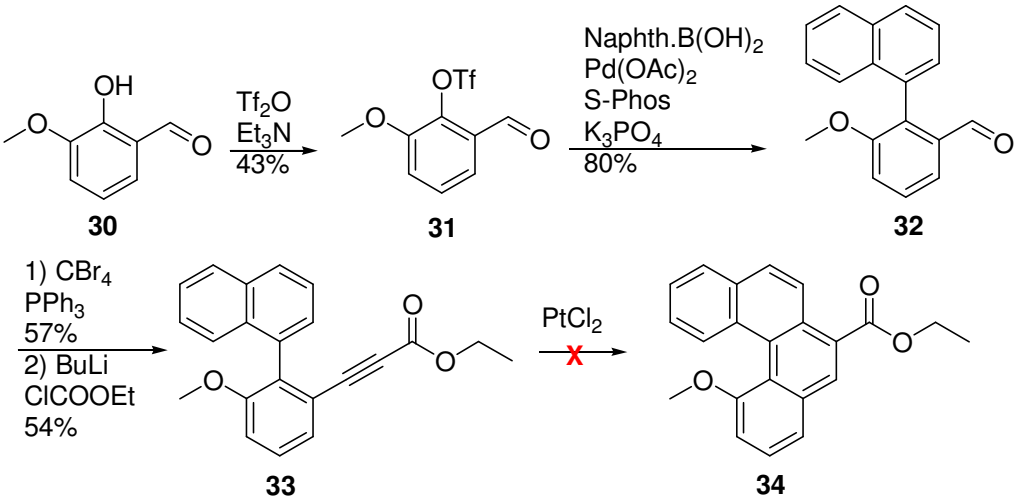
In the first step, tetralone **14** (the synthesis of which is described in chapter 4) is converted in moderate yield to phenol **15** via condensation with ethyl formate and subsequent oxidation[6]. Coupling with bromoethyl acetate[7] gave furan **16** in 71% yield. Saponification of the ester[8] gave acid **17**. Treatment with LDA[9], as described for several benzofuran derivatives, does initially seem to give the desired product, but, upon workup, the reaction gives back starting material **17** or, upon use of more forcing conditions, decomposition.

5.2.2 Double Suzuki strategies using acid functionalized alkynes



Scheme 6: Synthesis via acid functionalized benzo[c]phenanthrene

Another approach is that shown in scheme 6. The synthesis of compound **24** has been described in the literature[10,11] and was performed as such without problems. However Sonogashira coupling with ^{t}Bu propiolate[11] did not give the expected propiolic ester **26**, but gave instead reduction to alkene **27** (as a mixture of *E*- and *Z*-isomers), probably with a Et_3N/Pd –complex as hydrogen source[12,13]. To avoid this, we carried out a different approach (scheme 7) to prepare an ester similar to alkyne **28**:

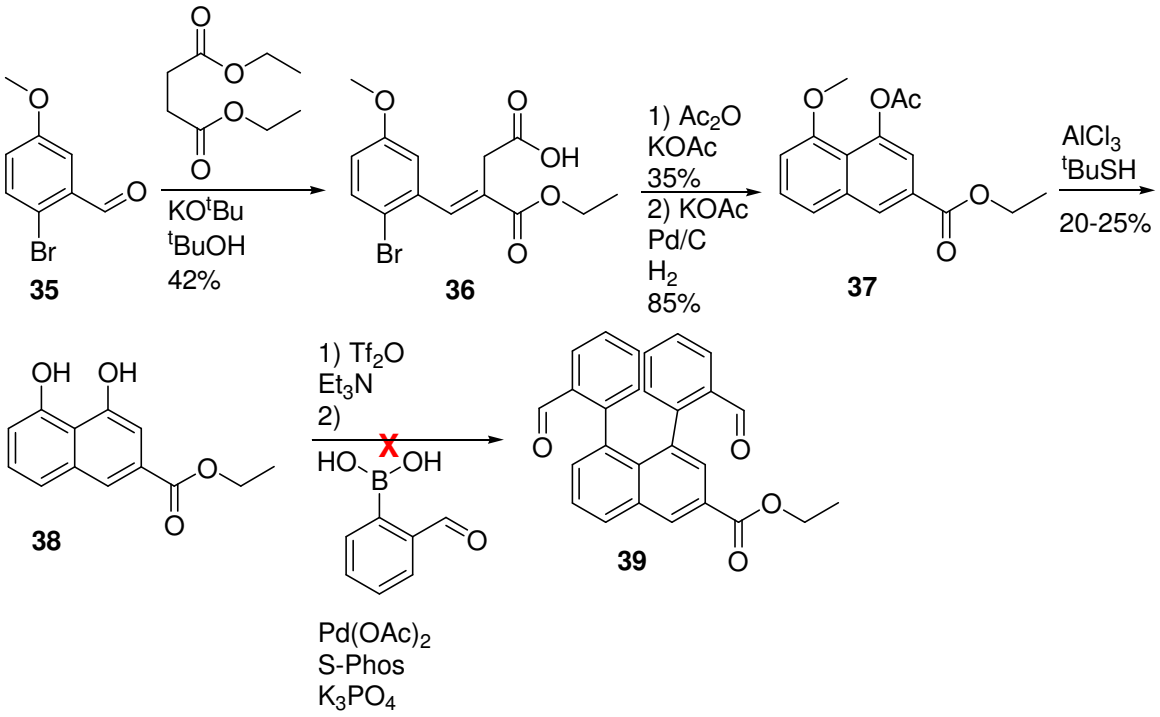


Scheme 7: Suzuki and subsequent alkyne formation

The triflate **31** of o-vanillin **30** was prepared and subjected to a Suzuki reaction, under the previously described conditions. In this case the aldehyde could be converted to the alkyne[14]. Unfortunately, ring closure was not successful and surprisingly, no conversion was observed using $PtCl_2$, while similar examples have been described in the literature[14]. The reason for this remains unclear.

We consider it possible that this was the reason for the failure of ring closure and therefore decided to change the strategy to one where the acid (or at least an anchor) is already in place.

5.2.3 Double Suzuki strategy using Stobbe condensation

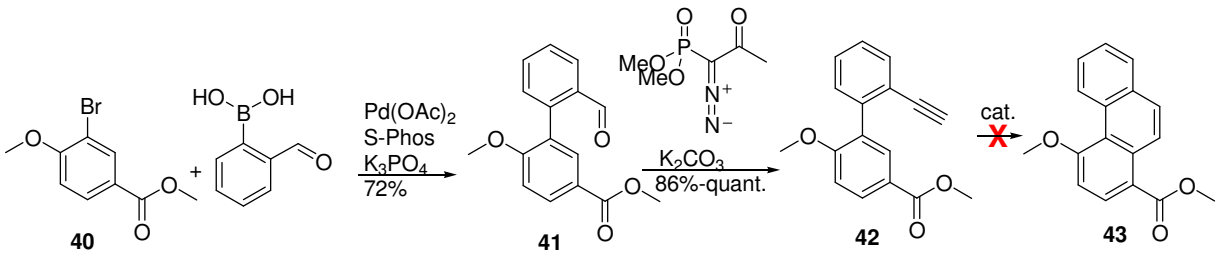


Scheme 8: A Stobbe-condensation route to a bisphenol naphthoic ester.

The first steps of the new approach (scheme 8), which would lead to 7-substituted hexahelicene are shown in scheme 8. In the first step, aldehyde **35** was condensed with diethyl succinate to give keto acid **36**[15,16], using the bromine to block the 2 position, and by doing so avoiding the formation of the 7-methoxy substituted naphthalene instead of the desired 5-methoxy regioisomer in the Stobbe-condensation. Ring closure[15] and removal of the bromine[17] "protective group" gave compound **37**. Deprotection of the methoxy and acetoxy groups was attempted in several different ways: 1. with HBr, 2. in a 2 step method, first removing the methoxy group with K_2CO_3 in EtOH and subsequently removing the methoxy group withBBr_3, or 3. Removing both protective groups with $AlCl_3$/^{t}BuSH[18]. The last method gave the best results. Some attempts were made to make the bis triflate, however, overall yields were so low, that we had to change the route for a higher yielding one.

5.2.3 Phenanthrenecarboxylic ester routes

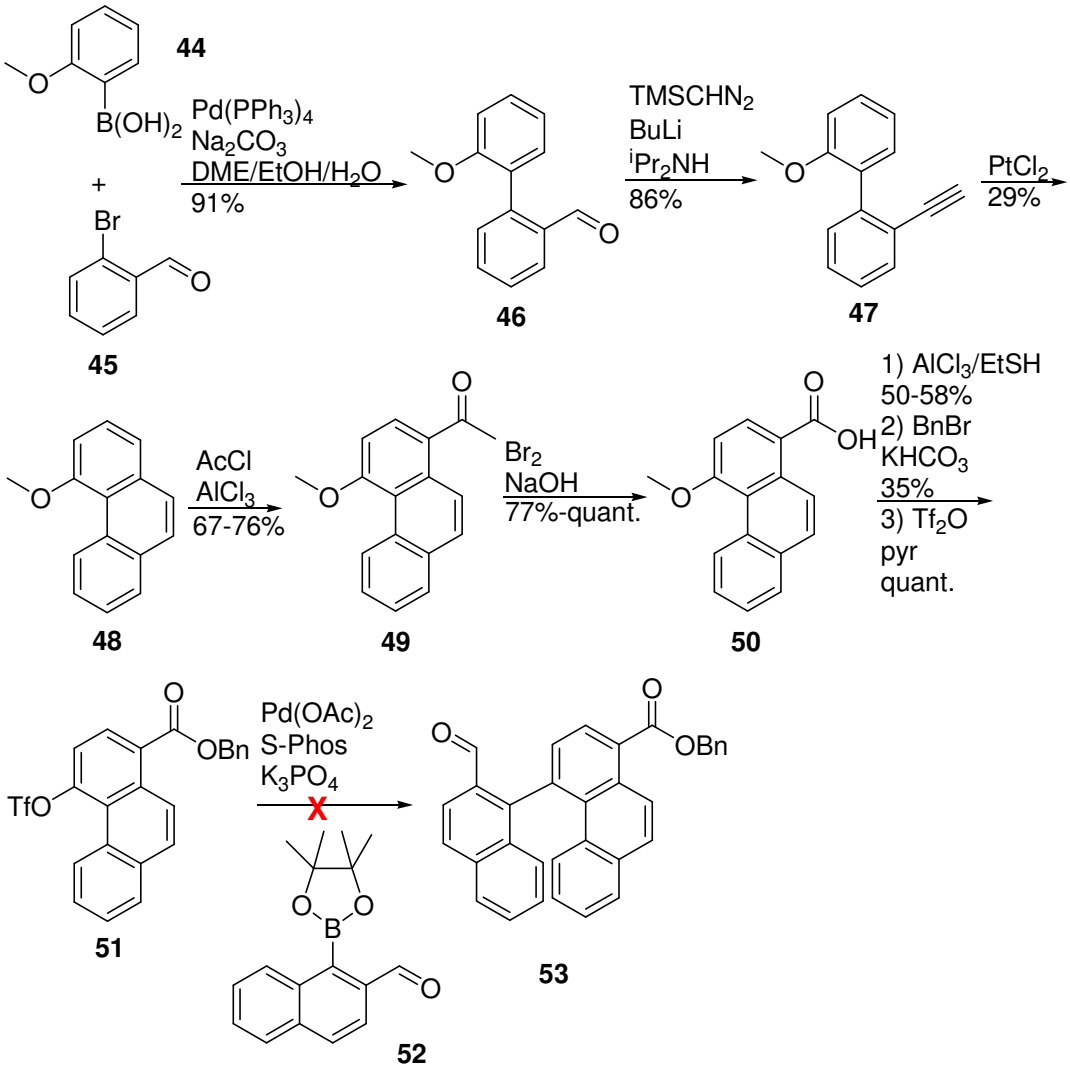
We then sought a route which would use two $PtCl_2$ catalyzed ring closure in order to start with smaller building blocks:



Scheme 9: Double $PtCl_2$ ring closing route

The starting steps are shown in scheme 9. In the first step, the Suzuki coupling gives the desired biphenyl **41** in good yield. This is then converted to alkyne **42** following the usual procedure. Ring closure was tested with $InCl_3$, $Ga(OTf)_3$, $[Ir(COD)Cl]_2$, $[(p\text{-}Cym)RuCl]_2$, $Rh(COD)_2BF_4$ and AuCl, but in all cases no (or very low) conversion was observed. As is the case with the route in scheme 7, this is probably again due to an electronic effect.

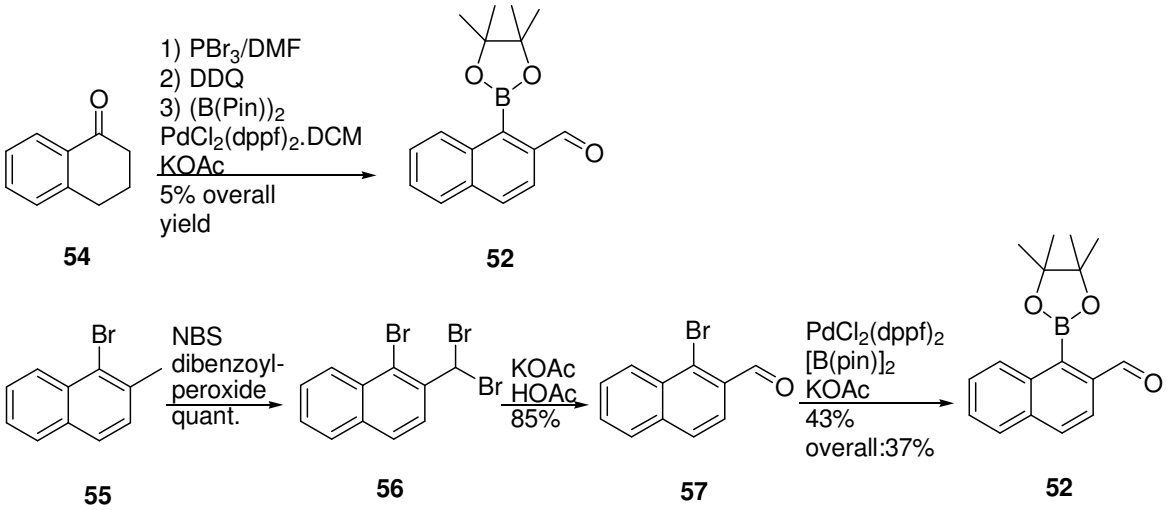
To circumvent this, we chose to introduce an acid functionality in the built up ring system as shown in scheme 10:



Scheme 10: First Friedel-Crafts strategy

The synthesis of phenanthrene **48** has been described in the literature[14] and except for the ring closing step, which proceeded in slightly lower yield, equivalent yields were obtained. Friedel-Crafts acylation on this compound has been reported[19] and worked well and very selectively, as did the subsequent haloform reaction, which allowed acid **50** to be isolated easily. We then sought to protect **50** as the benzyl ester and then subsequently remove the methoxy protective group with $AlCl_3$/dodecanethiol[20,21] or with 2-(diethylamino)ethanethiol[22]. In both cases the benzyl protective group was lost. Therefore we tried to deprotect acid **50** with HBr (led to

decarboxylation), with BBr_3[23](a very complex mixture was obtained, even though the reaction has been described for the naphthalene instead of the phenanthrene derivative), with $AlCl_3$/dodecanethiol[20,21] (product isolated in low yield), with $NbCl_5$[24](a mixture of starting material and side products is isolated) and finally with EtSH/$AlCl_3$. This final method worked, but yields decreased upon scale up. Also to work on large scale with large excesses of EtSH is very unpleasant. We managed to prepare some material and prepared the benzyl ester[25], converted this to the triflate and tested this in the Suzuki coupling with boronic ester **52**. This reaction failed. Ester **52** was prepared as depicted in scheme 11:

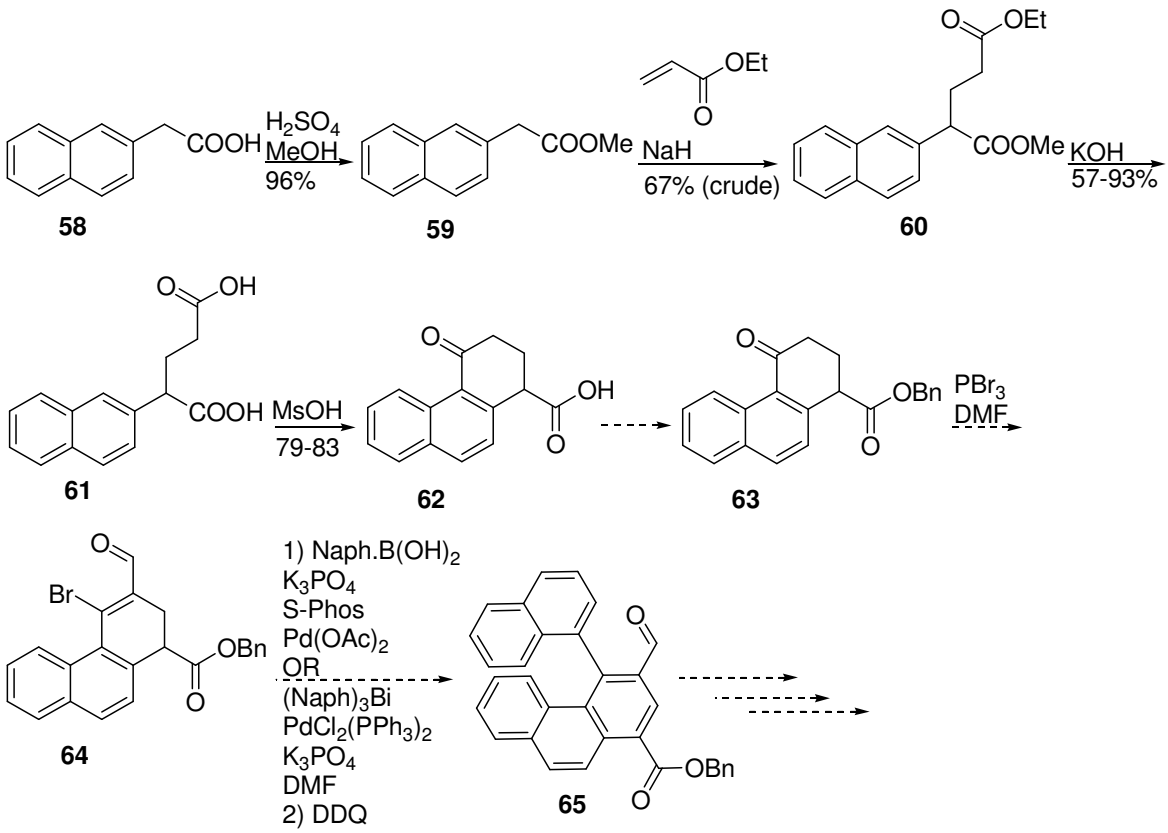


*Scheme 11: Synthesis of boronic ester **52***

At first boronic ester **52** was prepared, starting from tetralone **54**, by a Vilsmeier formylation, oxidation with DDQ and subsequent transborylation in only 5% overall yield. We then found that yield is greatly improved if the bromoaldehyde **57** is prepared from bromide **55**, by double bromination and conversion to the diacetate, which hydrolyses upon workup to give the desired aldehyde[26]. Trans-borylation then gives the desired boronic ester **52** in 37% overall yield.

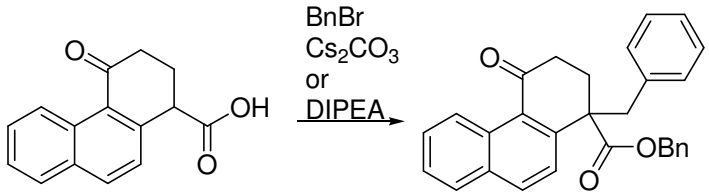
5.2.4 Michael addition route

However, since the Suzuki reaction did not work and the overall yield was low and there were problems in the methoxy deprotection, we decided to change the route again as shown in scheme 12:



Scheme 12: Michael addition route

In this route, we started from acid **58** and performed a esterification[27] and subsequent Michael addition, which we found worked best with NaH as a base. Saponification with KOH[28] gave diacid **61**.The ring closure on this compound has been described using anhydrous HF[29]. However, we found that ring closure with MsOH also gave ketoacid **62** in good yields. Attempts were made to protect the acid with BnBr, but the desired ester **63** was not isolated. Instead, as shown in scheme 13, dibenzyl compound **66** was isolated as sole product when two eq. of BnBr are used (we did expect the benzyl enol ether and therefore thought two eq. were necessary), or as a mixture of acid **62** and dibenzyl compound **66** when one equivalent is used.



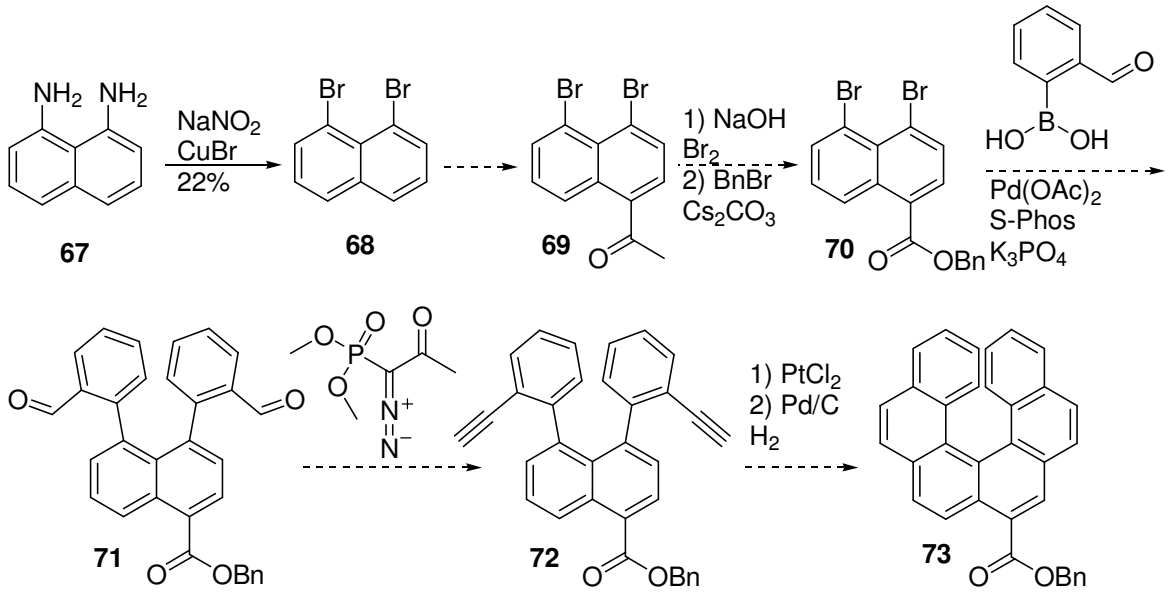
62 **66**

*Scheme 13: Esterification of ketoacid **62***

We also tried to to prepare ester **63** *via* a peptide coupling with BnOH, EDCI, HOBt and Et_3N, but this gave no conversion. We were able to prepare the desired acid by making the acid chloride with oxalylchloride and a drop of DMF. The acid chloride was then allowed to react with BnOH and pyridine[30] to give the benzyl ester **63**. This benzyl ester did not give the desired product in the Vilsmeier reaction to aldehyde **64** but instead gave decomposition. We were, however, able to make the bromo aldehyde from compound **62** (compound **64** without benzyl ester) and tested this in a Suzuki reaction and in a coupling with trinaphthylbismuth[31], prepared from naphthylbromide[32], but neither the Suzuki nor the coupling with the bismuth reagent worked, possibly due to degradation of the bromide.

5.2.5 Dihalide double Suzuki reaction

We then considered application of the Friedel-Crafts strategy to another scaffold:



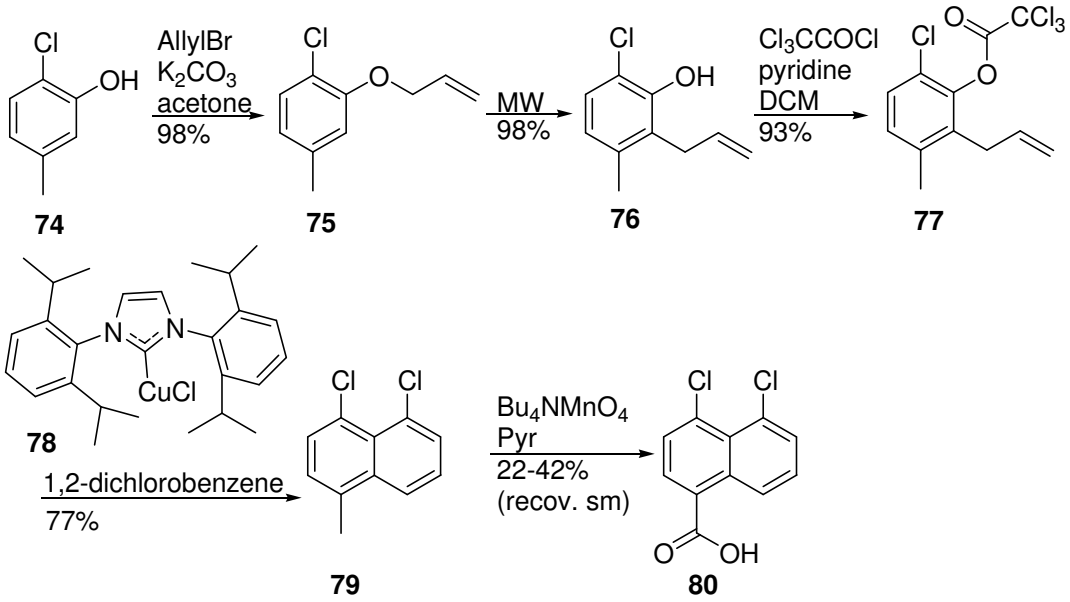
Scheme 14: 2nd Friedel-Crafts approach

For this route we envisaged to make a 1,8-dibromonaphthalene, for which Suzuki reactions are well known[e.g. 33,34,35]. To make dibromide **68** a catalytic Sandmeyer bromination[36] was first tested, but in our hands, this did not work. A classic Sandmeyer reaction[37] was carried out to give dibromide **68** in 22% yield. The Friedel-Crafts reaction has been described for 1-bromonaphthalene[38], 1,8-dichloronaphthalene[39] and for 1,8-difluoronaphthalene[40]. However, in the case of dibromide **68**, a range of conditions was tested (see table 1) without leading to really satisfactory results:

Conditions	Yield of 69
AcCl, $AlCl_3$/LiCl/DCE -30°C → RT[40,41]	12% isolated
AcCl, $AlCl_3$/LiCl/DCE -30°C → RT	Ca 10%
AcCl, $AlCl_3$/LiCl/DCE -40°C → -20°C	Same or worse
AcCl, $AlCl_3$/DCE RT → reflux	Ca 20%
AcCl, $AlCl_3$/$MeNO_2$ 0°C → RT	Starting material
AcCl, $AlCl_3$/$MeNO_2$ 0°C → 100°C	Starting material
AcCl, $AlCl_3$/LiCl/$MeNO_2$ -30°C → RT	Starting material
AcCl, ZnO, neat, RT[42]	Starting material
HOAc, MsOH, 80°C	Condensation or
AcCl, $NbCl_5$, DCE 0°C → 100°C[43]	Ca 20%
Ac_2O, $InCl_3$, $AgClO_4$,CH_3CN, 50°C[44]	Starting material
Ac_2O, BF_3.OEt_2, toluene, RT[45]	Starting material

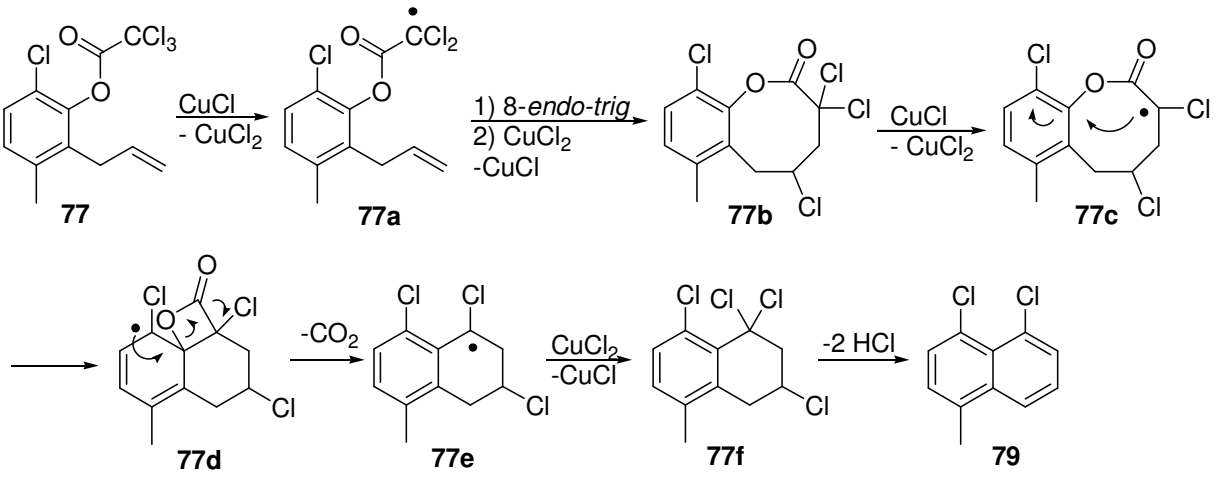
Table 1: Friedel-Crafts reaction on 1,8-dibromonaphthalene

The explanation for the problems in this reaction might be that a "halogen dance" occurs as has been described, for instance, for 4,5-dichloro-1-naphthoic acid with $AlCl_3$/NaCl/HCl and heat[46] and for 1,8-dibromonaphthalene at 290°C with HCl[47]. This reaction is expected to give more problems when the carboxylic acid is introduced. Considering this and the low yields in the Sandmeyer- and Friedel-Crafts reactions, we changed the route to the dichloride instead of the dibromide and with a handle in place to introduce the acid without the need for a Friedel-Crafts reaction.



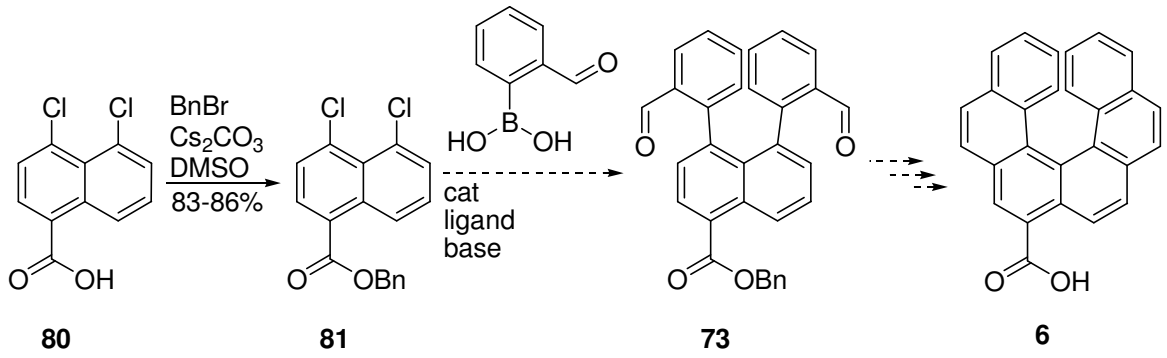
Scheme 15: synthesis of dichloronaphthoic acid

The synthesis of compound **76**has been described in literature[48] in almost quantitative yield. Reaction with trichloroacetyl chloride and subsequent ring closure with catalyst **78**[49] gave dichloroarene **79** in 69% overall yield starting from phenol **74**. The proposed mechanism is depicted in scheme 16[49,50].



*Scheme 16: Mechanism for ring closure of compound **77**.*

The ring closure was not performed in the microwave as described in the literature due to the limited volume in the microwave vials and the dangers of metal catalyst deposition on the side of the vial and subsequent super-heating. We therefore successfully performed the reaction with conventional heating in 1,2-dichlorobenzene with comparable yields. Oxidation of compound **79** has not been described in the literature. We therefore first tested a classical $KMnO_4$ oxidation in aqueous NaOH[51]. However due to insolubility, no reaction was observed. Changing the solvent to a mixture of water and ^tBuOH[52] improved the yield to ca 15%. However, we felt that the lack of solubility still was an issue. Changing to oxidation with CrO_3 in H_2SO_4/HOAc[53] gave also only starting material. We then turned back to a permanganate oxidation and looked for a compound which is more soluble in organic solvents. We found $(n\text{-}Bu)_4NMnO_4$[54,55] to be soluble in pyridine, but it has not been used widely in organic chemistry. We prepared this reagent and used it in the oxidation[54] and got around 40% yield. In some cases the $(n\text{-}Bu)_4NMnO_4$ seems to deteriorate after some time (perhaps due to impurities left in the material). When this material is used, the yield drops to ca 20% and more starting material is recovered. The melting point of acid **80** was in agreement with literature data[56].

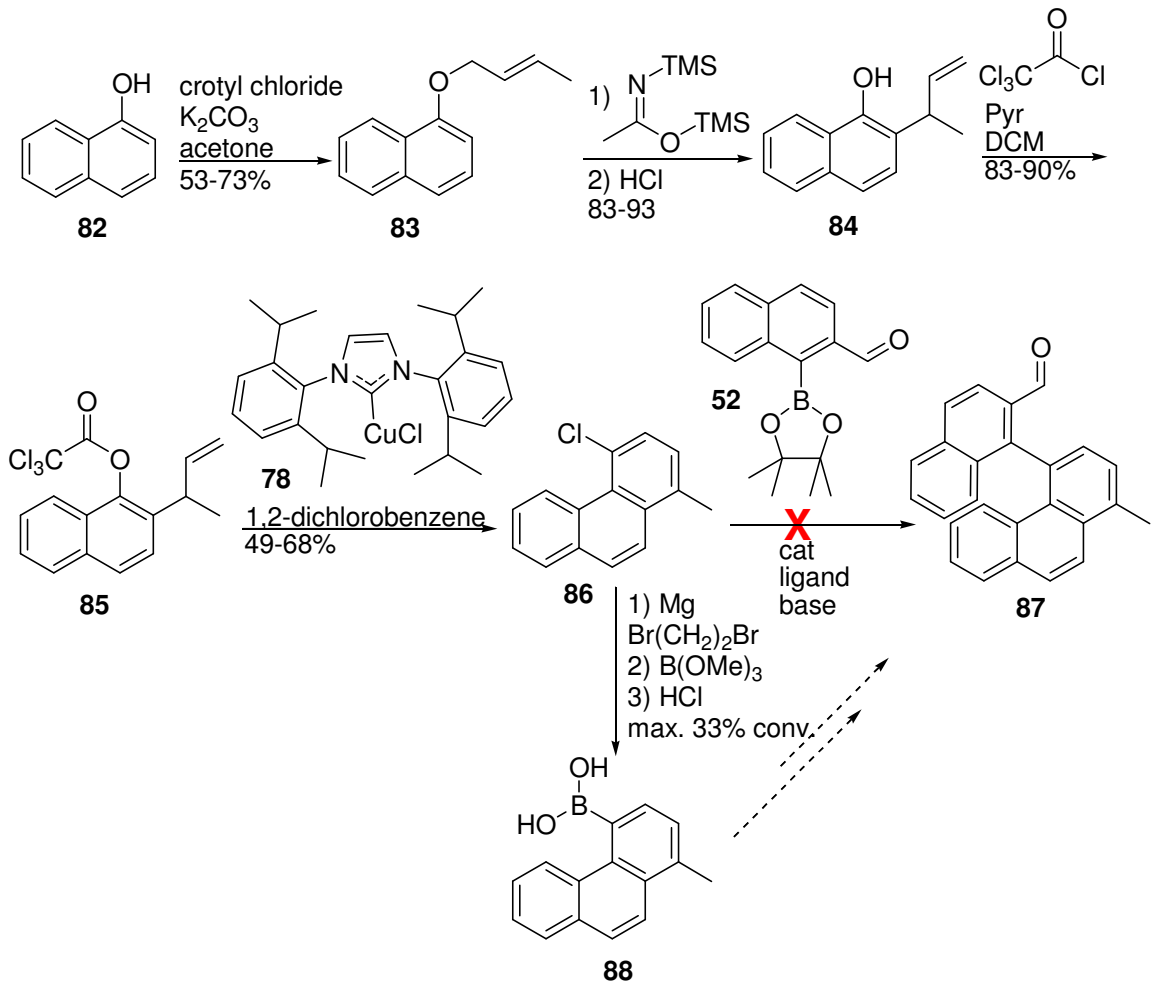


Scheme 17: Double Suzuki strategy

As can be seen in scheme 17, esterification of acid **80** was successful and gave benzylester **81** in good yields. However in our hands we were not able to get a double Suzuki reaction on compound **81**. Usually mixtures of starting material, mono-Suzuki product and (partially) dehalogenated materialwere obtained. Protection of the aldehydes as acetals or use of ligands specially designed for sterically demanding (double) Suzuki reactions[57,58,59] or use of nickel catalysts did not give improvement. Also a Kumada coupling on compound **80**[60] did not give the desired selectivity.

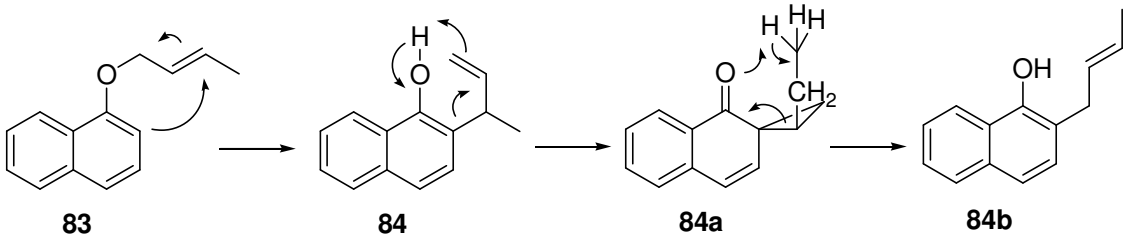
5.2.6 Methylphenanthrene routes

We then thought of adapting the copper-catalyzed ring closure in such a way that only one Suzuki reaction is necessary. The route is depicted in scheme 18.

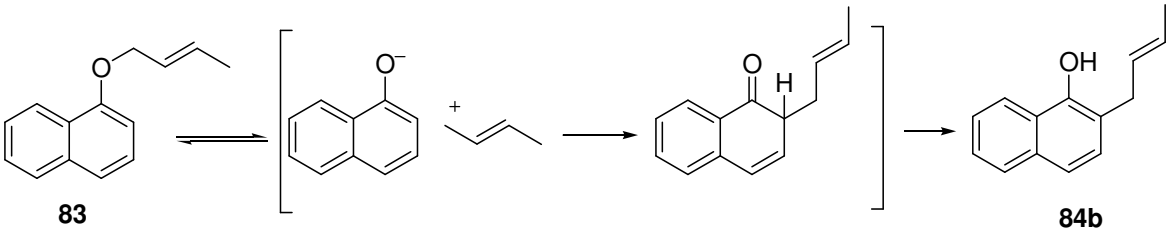


Scheme 18: methylphenanthrenechloride approach

In the first step 1-naphthol **82** is allowed to react with crotylchloride to give crotyl ether **83**. Reaction with crotylbromide gives slightly higher yield, but also leads to some small impurities which in our hands could not be removed, even in later steps. For the Claisen rearrangement, there were initial problems with regioselectivity whereby the linear alkene **84b** was also obtained. Two possible mechanisms are depicted in schemes 19 and 20.[61]



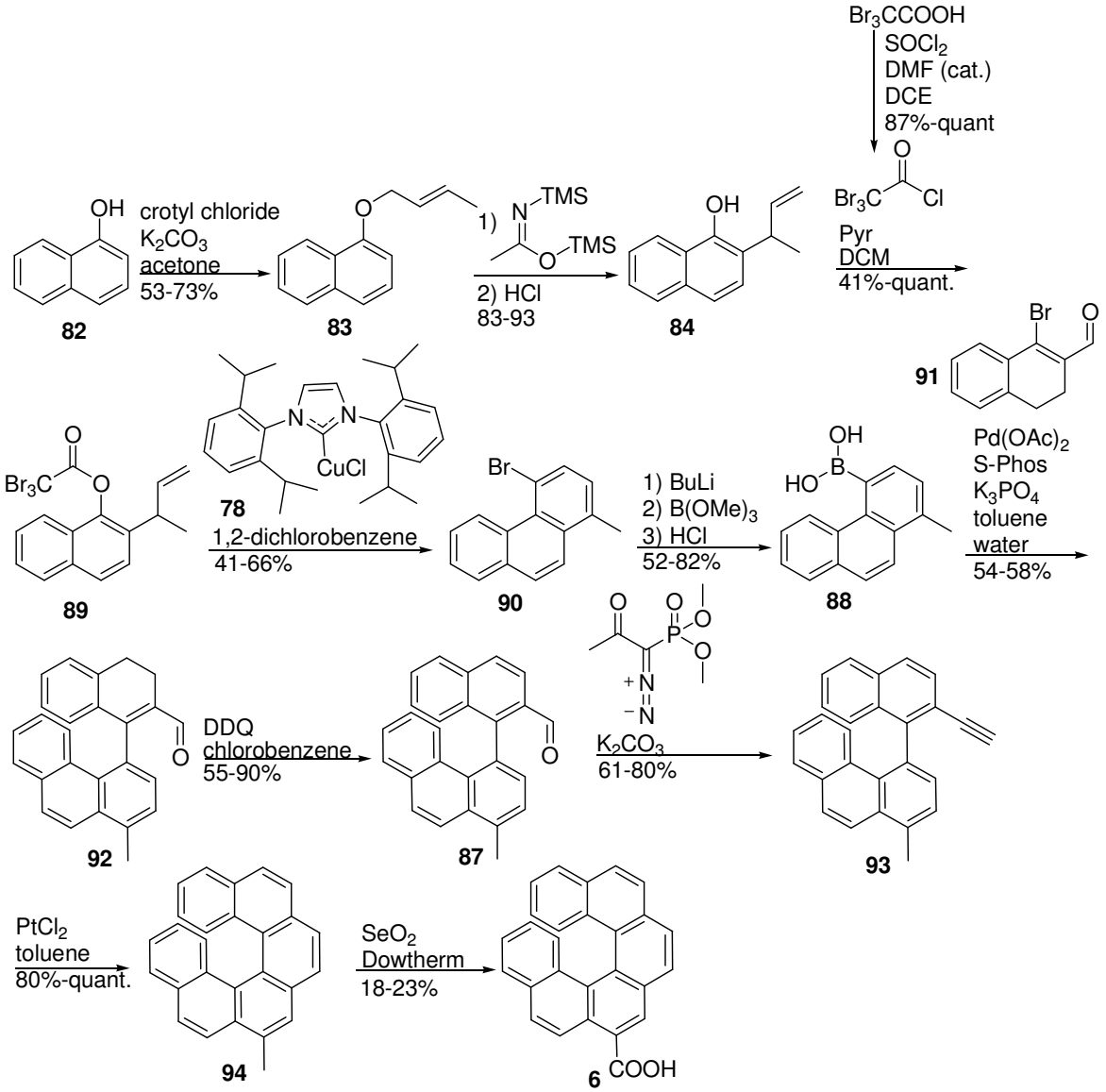
Scheme 19: First possible mechanism of Claisen side product formation



Scheme 20: Second possible mechanism of Claisen side product formation

After testing $SnCl_4$ in DCM[62], BCl_3 in DCM[63], MW heating (neat)[48], TFA[61] and $Eu(FOD)_3$ in $CHCl_3$[64]a paper was found describing the use of *N*,*O*-bis(trimethylsilyl)acetamide, which prevents the abnormal Claisen rearrangement[65]. This worked beautifully and gave indeed only the desired product **84** upon hydrolysis of the TMS-protected phenol in 83-93% yield. From this phenol, methylchlorophenanthrene **86** was prepared in two steps. Unfortunately Suzuki reaction of compound **86** with boronic ester **52** did not work in our hands. We therefore wanted to perform the reaction the other way around and tried to convert chloride **86** in boronic acid **88** (see scheme 18). We found, however, that standard chlorine-lithium exchange or chlorine-magnesium exchange in the microwave[66] was not possible. The so-called entrainment method[67] using the slow addition of dibromoethane to a mixture of the arylchloride and magnesium did give ca 34% conversion, but for us this was not satisfactory.

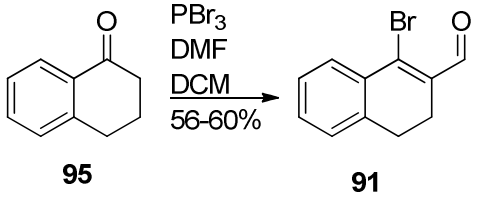
Therefore we decided to make the bromide-derivative of compound **86** instead of the chloride (see scheme 21):



*Scheme21: final route to hexahelicenecarboxylic acid **6**.*

In this case, because of the larger scale, catalyst **78** was prepared according to literature procedures[68,69]. The formation of tribromoacetylchloride was a bit trial and error; NMR analysis is not possible, carbon NMR is not very clear and GC analysis was not possible. We could only test whether the chloride was formed by performing the next reaction. In this way we found that reflux in DCM leads to no conversion at all, DCE is needed to get conversion. The copper-catalyzed ring closure gave somewhat lower yield than in the case of the chloride due to dehalogenation.

The bromo-lithium exchange from **89** to **90** worked fine and gave boronic acid **90** in 52-82% yield. For the Suzuki reaction, bromoaldehyde **91** had to be prepared. This was done using the step depicted in scheme 22.



*Scheme 22: Synthesis of bromoaldehyde **91***

Alpha-tetralone **95** was treated with PBr_3 and DMF in DCM to give bromoaldehyde **91** in 56-60% yield. The quality of the tetralone was of great importance for the yield. When a batch prepared in China was used, only 20-30% yield was obtained, whereas a batch from Acros gave the mentioned higher yield. Suzuki coupling of boronic acid **90** and bromoaldehyde **91** gave at first Suzuki product **92** in reasonable yields. Due to the high cost of the ligand we decided to test if we could lower the catalyst loading. Also we tested twelve different conditions, varying solvent between toluene/water and dioxane, and changing ligand and base. The only system that could compete with the conditions depicted in scheme 20 was using $PdCl_2(dppf)_2$.DCM and Cs_2CO_3 in toluene/water. The results of the catalyst loading and of the choice of the system are depicted in table 2:

Notebook Page	Yield 92	Cat/ligand	Amount cat	Amount ligand	Notes
160117	60%	$Pd(OAc)_2$/S-Phos	3%	7%	
160127	48%	$Pd(OAc)_2$/S-Phos	3%	7%	
160153	48%	$Pd(OAc)_2$/S-Phos	3%	7%	
160173	18-26%	$Pd(OAc)_2$/S-Phos	2%	3%	
160182	15%	$Pd(OAc)_2$/S-Phos	2%	3%	
160193	31%	$Pd(OAc)_2$/S-Phos	2%	3%	Not pure
160198	62%	$Pd(OAc)_2$/S-Phos	5%	12,5%	
160180	16%	$PdCl_2(dppf)_2$.DCM	2%		
160194	43%	$PdCl_2(dppf)_2$.DCM	2%		Not pure
160195	41%	$PdCl_2(dppf)_2$.DCM	3%		Not pure
160199	41%	$PdCl_2(dppf)_2$.DCM	10%		Not pure

*Table 2: Suzuki reaction to compound **92***

As can be seen in table 2 the best results are obtained with a somewhat higher catalyst loading using S-Phos as the preferred ligand. If the catalyst loading was too low, and in the case where $PdCl_2(dppf)_2$.DCM was used as a catalyst, a side product was formed, which could not be removed in this stage, but only after the next step resulting in a significant lowering of the overall yield.

Oxidation of **92** with DDQ was at first troublesome. When the same conditions as for the aminohelicene are used (reflux in benzene) the reaction takes several weeks to go to full conversion. When dichlorobenzene is used at 130°C (externally), the reaction is finished within 2 h. but some side products are formed. When refluxing toluene is used, the reaction takes ca. overnight and is somewhat cleaner than in DCB, but still side products can be seen. When chlorobenzene at 130°C (externally) is used, the reaction is finished in 2 h and is clean. In the literature, there was an example in which reaction in chlorobenzene is at least in one case faster than in benzene[70], but it is also mentioned that a correlation between oxidation speed and solvent properties is not trivial[71], although both cases cited were oxidations of alcohols instead of aromatization. The obtained product can then be converted without problems to the desired alkyne **93** as long as during the work up, the mixture is washed with aqueous NaOH. If this is omitted, in the next step the dimethyl acetal instead of the alkyne is isolated. Subsequently ring closure is performed using $PtCl_2$ to give methylhelicene **94** in 63%-quantitative yield.

The structure of this compound was confirmed by X-ray analysis and is depicted in figure 2. The spacegroup is $P2_1/c$ and is therefore a racemic compound rather than a conglomerate. The

structural work was performed by Dr. Klaus Wurst of the University of Innsbruck. The mass was determined by Theodora Tiemersma-Wegman of the University of Groningen.

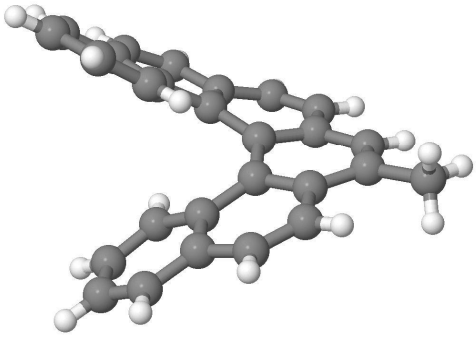


Figure 2: X-ray structure of 7-methylhexahelicene

Oxidation to the final product **6** proved difficult, as was to be expected to some extent based on the literature[72]. Ring oxidation and cleavage can be competing processes. Many different methods were tested: $(n\text{-}Bu)_4NMnO_4$[54,55], $CrO_3/H_2SO_4/HOAc$[53], $KMnO_4$/pyridine/water[73,74], $KMnO_4$ in butanone or acetone[75], $KMnO_4$/dicyclohexyl-18-crown-6 in benzene[76], $HBr/O_2/hv$[77], $RuCl_3.3H_2O/NaIO_4$ in CCl_4/CH_3CN/water[78], DDQ (oxidation to the aldehyde)[79], CAN in MeOH (oxidation to the aldehyde)[80]. Since the oxidation of several methylbenzophenanthrenes have been described using $Na_2Cr_2O_7.2\ H_2O$ in water at 250°C[81] (conditions not possible to perform at Syncom BV), we also tested external high temperature oxidation using $KMnO_4$ or $Na_2Cr_2O_7.2H_2O$ in Dowtherm at 250°C but obtained no conversion at all. The use of $(n\text{-}Bu)_4NMnO_4$ in pyridine led to some conversion (ca. 10%). Decomposition of the salt likely occurs before the reaction is complete. Since in the literature it has been described that coating the permanganate compound on Alox can improve the stability of tetraalkylammonium permanganates[82], we also tested this but with similar low conversions. The only approach that worked reasonably was the use of SeO_2 in Dowtherm A at 260°C (externally) in an open system while blowing a flow of air over the mixture to remove the water formed during the reaction. A mixture of aldehyde and carboxylic acid was obtained. At lower temperature, only the aldehyde was obtained. If the temperature was raised, then a substantial amount of decomposition products was obtained. Attempts to improve the conversion by addition of K_2CO_3 in pyridine or Dowtherm[83] did not help. Attempts were made to oxidize the obtained aldehyde to the carboxylic acid with $NaBO_3.4H_2O$ in HOAc[84], H_2O_2/K_2CO_3 in MeOH[85], CrO_3 in H_2SO_4[86] and even SeO_2 in Dowtherm at 260°C (externally) in an open vessel but no conversion was obtained in any of these cases. Purfication of the reaction

mixture was difficult. At first, suitable column chromatographic conditions could not be found and preparative HPLC was tested. This gave serious solubility problems and the recovery was very low. We then converted the acid in the crude mixture to the benzyl ester with Cs_2CO_3 and BnBr in CH_3CN at reflux and were able to isolate pure benzyl ester. However, removal of the benzyl group using an H-Cube© at 50°C and 100 bar of H_2 gave incomplete conversion and finally decomposition. More or less acceptable purification by column chromatography over SiO_2 was eventually possible, using 20% acetone in toluene. This gives mainly mix-fractions and some pure fractions. The pure fractions were used for STM-analysis.

5.3 Summary and Conclusions

After more than expected effort, the synthesis of a hexahelicene with an acid functionality at the 7-position has been accomplished. Owing to difficulties in the final step, oxidation of 7-methylhexahelicene to the desired carboxylic acid, the synthesis is not yet readily scalable. The unsuccessful routes summarized in the initial part of the chapter provide considerable insight in the delicate balances that must be maintained during a complex synthesis.

We conclude that a successful synthesis has been achieved. If the final oxidation step can be improved, scale up should be possible. The initial experiments to attach the material to surfaces are promising but not yet conclusive.

5.4 Experimental Section

(*E*)-1-(but-2-en-1-yloxy)naphthalene (84). 1-Naphthol **83** (200 g, 1.4 mol), crotyl chloride (predominantly trans, 149 mL, 1.53 mol, 1.1 eq.) and K_2CO_3 (211 g, 1.53 mol, 1.1 eq.) were heated for 3 days at 80°C (ext.) in acetone (5L), divided over 2 flasks. After NMR-analysis revealed complete conversion, the recombined mixture was filtered and concentrated and the residue was filtered over SiO_2 (heptane) to give ether **84** (204 g, 73%) as a yellow oil, which was used without further purification in the next step.

^{1}H NMR ($CDCl_3$) δ8.30 (dd, 1H), 7.79 (dd, 1H), 7.33-7.51 (m, 4H) 6.83 (d, 1H), 5.80-5.99 (m, 2H), 4.78 (*cis*, d <1H), 4.65 (*trans*, d, 2H), 1.80 (m, 3H)

^{13}C NMR ($CDCl_3$) δ154.9, 135.0, 130.2, 128.7, 127.8, 126.7, 126.6, 126.2, 125.5, 122.6, 120.6, 105.4, 69.2, 64.5 (small, *cis*), 18.3

[M](GC/MS) calculated: 198.10 found: 198.1

2-(but-3-en-2-yl)naphthalen-1-ol (85). Crotyl ether **84** (204 g, 1.0 mol) and *N*,*O*-bis(trimethylsilyl)acetamide (255 mL, 1.0 mol, 1 eq.) were heated at reflux for 30 min. After NMR-analysis revealed complete conversion, 3N HCl (2 L) was added and the resulting mixture was extracted twice with Et_2O (2L, 1L). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was stirred for 30 min with a mixture of MeOH (1.75 L) and 3 N HCl (1.25 L) after which Et_2O (5 L) was added. The layers were separated and the organic layer was washed with brine (1 L), dried over Na_2SO_4 and concentrated. To the residue was added water (1 L) and the resulting mixture was extracted with heptane (2 L, 1L) and the combined organic layers were washed with water (2x 1L), dried over Na_2SO_4 and concentrated to give phenol **85** (171.2 g, 84%) as an orange oil, which was used without further purification in the next step.

^{1}H NMR ($CDCl_3$) δ8.18 (m, 1H), 7.78 (m, 1H), 7.45 (m, 3H), 7.27 (d, 1H), 6.14-6.25 (m, 1H), 5.73 (s, 1H), 5.31 (m, 2 H), 3.78 (m, 1H), 1.51 (d, 3H)

^{13}C NMR ($CDCl_3$) δ149.3, 142.5, 133.8, 127.7, 126.4, 126.1, 125.6, 125.4, 123.1, 121.8, 120.7, 115.3, 38.9, 18.8

[M](GC/MS) calculated: 198.10 found: 198.2

2-(but-3-en-2-yl)naphthalen-1-yl 2,2,2-tribromoacetate (86). Tribromoacetic acid (296.7 g, 1 mol) and $SOCl_2$ (145 mL, 2 mol, 2 eq.) and a few drops DMF were heated overnight at reflux in DCE (2 L). The mixture was evaporated and stripped with toluene to give tribromoacetylchloride (311 g, 99%) as a dark oil, which was used as such.

To phenol **85** (171.2 g, 864 mmol) in DCM (2 L) was added at 0°C pyridine (80 mL, 987 mmol, 1.14 eq.) and then tribromoacetyl chloride (311 g, 987 mmol, 1.14 eq.) dropwise. After stirring at 0°C for 1 h., NMR-analysis revealed complete conversion and the mixture was washed with 1 M citric acid (2x 1.5 L), dried over Na_2SO_4 and concentrated to give ester **86** (425.5 g, quant., contains some DCM) as a red oil which was used without purification in the next step.

^{1}H NMR ($CDCl_3$) δ7.98 (d, 1H), 7.79-7.88 (m, 2H), 7.48-7.59 (m, 2 H), 7.42 (d, 1H), 6.01-6.12 (m, 1H), 5.12-5.18 (m, 2H), 3.96-4.00 (m, 1 H), 1.43 (d, 3 H)

^{13}C NMR ($CDCl_3$) δ160.9, 141.4, 134.1, 133.6, 129.3, 128.5, 128.3, 127.8, 127.5, 126.5, 125.4, 120.9, 114.8, 36.1, 27.9. 20.0

[M+NH_4^+](API/ES) calculated: 491.88 found: 491.71

4-bromo-1-methylphenanthrene (90). Tribromoacetyl ester **86** (121.8 g contains some solvent, max. 432 mmol) in DCB (300 mL) was bubbled through with N_2 for 10 min. Copper catalyst **79** (5.7 g, 11.7 mmol, 2.7%, prepared according to literature procedures[68,69]) was added and the mixture was heated at reflux for 40 min. After NMR analysis revealed complete conversion, DCB was removed by bulb-to-bulb distillation using a membrane pump. The resulting mixture was coated on SiO_2 (400 mL) and filtered over a plug of SiO_2 (1 L, heptane) to give bromide **90** (0.7 g, 52%) as an orange solid which contains debrominated product (ca 23%). This material is easily removed after the next step. For analytical reasons a sample was purified by column chromatography over SiO_2 (heptane)

^{1}H NMR ($CDCl_3$) δ9.96 (m, 1H), 7.89 (m, 3H), 7.79 (d, 1H), 7.61-7.66 (m, 2H), 7.25 (d, 1H), 2.71 (s, 3H)

^{13}C NMR ($CDCl_3$) δ134.9, 134.2, 133.9, 133.2, 130.3, 128.9, 128.5, 128.4, 128.2, 127.4, 127.2, 125.3, 123.0, 117.3, 20.5

M](GC/MS) calculated: 270.00 found: 270.0

(1-methylphenanthren-4-yl)boronic acid (91). To bromide **90** (60.7 g, 224 mmol) in a flame dried flask in dry THF (1 L) was added at -78°C BuLi (2.5 M in hexanes, 103 mL, 257 mmol, 1.15 eq.). After stirring 1 h at -78°C, NMR analysis of a sample revealed complete conversion and $B(OMe)_3$ (51.7 mL, 470 mmol, 2.1 eq.) was added in one portion. The resulting mixture was stirred 30 min at -78°C and 1,5 h. at RT and was subsequently poured in 10% HCl (1.6 L). The mixture was extracted with Et_2O (2.5 L) and the organic layer was washed with water (2 L), dried over Na_2SO_4 and concentrated. The residue was triturated from heptanes to give boronic acid **91** (43.6 g, 82%) as a off white solid.

^{1}H NMR ($CDCl_3$) δ8.48-8.51 (m, 1H), 7.88, (d, 1H), 7.91 (m, 1H), 7.80 (d, 1H), 7.70 (d, 1H), 7.61 (m, 2H). 7.44 (d, 1H), 4.72 (bs, 2H), 2.76 (s, 3H)

^{13}C NMR ($CDCl_3$) δ136.7, 132.9, 132.7, 131.5, 131.3, 131.1, 128.8, 127.5, 127.2, 126.9, 126.8, 126.6, 126.3, 126.2, 123.3, 20.4

[M+Na](API/ES) calculated: 259.09 found: 259.12

1-bromo-3,4-dihydronaphthalene-2-carbaldehyde (92). To dry DMF (104 mL, 1.34 mol, 3 eq.) in dry DCM (1.8L) was added dropwise PBr_3 (106 mL, 1.12 mol, 2.5 eq.) at 0°C. α-Tetralone (60 mL, 447 mmol) was added and the mixture was allowed to warm to RT overnight. The mixture was heated at reflux for 3 h., then poured in ice (600 mL), giving a violent reaction. The mixture was made basic with saturated aqueous $NaHCO_3$. The mixture was extracted with Et_2O (3x 800 mL)

and the combined organic layers were washed with water (400 L), dried over Na_2SO_4 and concentrated to give 76.3 g crude **92** as a brown oil. The crude material was filtered over ca 500 mL SiO_2 (toluene) to give bromoaldehyde **92** (74.6 g, 70%) as an orange oil. The obtained material is NMR pure, but some minor, dark impurities can be removed by column chromatography over SiO_2 using EtOAc : heptanes 1 : 9 as eluting agent, giving an orange oil, which crystallizes upon standing.

^{1}H NMR ($CDCl_3$) δ10.26, (s, 1H), 7.90 (m, 1 H), 7.35 (m, 2H), 7.19 (m, 1H), 2.84 (t, 2 H), 2.62 (m, 2H)

^{13}C NMR ($CDCl_3$) δ193.4, 139.3, 134.8, 133.3, 131.6, 129.0, 127.8, 127.4, 27.4, 23.1

[M+1](API/ES) calculated: 236.98 found: 236.99

1-(1-methylphenanthren-4-yl)-3,4-dihydronaphthalene-2-carbaldehyde (93). A solution of bromide **92** (16.7 g, 71 mmol, 1 eq) in toluene (400 mL) and water (1 mL) was bubbled through with N_2 for 10 min. K_3PO_4 (30 g, 141 mmol, 2 eq.), boronic acid **91** (16.6 g, 71 mmol), $Pd(OAc)_2$ (792 mg, 3.5 mmol, 5%) and S-Phos (3.62 g, 8.8 mmol, 12.5%) were added and the mixture was heated at reflux overnight. After NMR-analysis revealed complete conversion, water (1 L) was added and the mixture was extracted with DCM (1L, 500 mL, 300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc : heptanes 1 : 9) to give aldehyde **93** (13.4 g, 54%) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ9.49 (s, 1 H), 8.61 (d, 1 H), 8.07 (d, 1 H), 7.85 (m, 2 H), 7.43-7.53 (m, 2H), 7.21-7.34 (m, 3H), 6.91 (t, 1 H), 6.74 (d, 1H), 3.08-3.17 (m, 2H), 2.76-2.93 (m, 2H), 2.86 (s, 3H)

^{13}C NMR ($CDCl_3$) δ193.5, 158.2, 139.0, 136.2, 134.9, 133.3, 133.2, 132.4, 131.5, 131.0, 130.6, 130.3, 128.9, 128.2, 127.6, 127.3, 127.2, 126.6, 126.0, 123.3, 27.7, 20.8, 20.6

[M+1](API/ES) calculated: 349.15 found: 349.2

1-(1-methylphenanthren-4-yl)-2-naphthaldehyde (88). Suzuki product **93** (6 g, 17.2 mmol) and DDQ (11.7 g, 51.7 mmol, 3 eq.) were heated at 120°C (ext) for 2 hours in chlorobenzene (100 mL). After NMR-analysis revealed complete conversion, the mixture was filtered over celite and washed with toluene. The resulting mother liquor was washed with 1 M NaOH (3x 300 mL) and the combined aqueous layers were washed with toluene (300 mL) and $CHCl_3$ (300 mL, 2x 150 mL). The combined organic layers were washed with water (300 mL), dried over Na_2SO_4 and concentrated to give 6.1 g crude **88** as a black oil. The obtained material was purified by column chromatography over 360 mL SiO_2 (EtOAc : heptanes 1 : 9) to give pure aromatized product **88** (3.3 g, 55%) as a yellow oil which solidified.

^{1}H NMR ($CDCl_3$) δ9.72 (s, 1H), 8.14 (t, 2H), 8.05 (d, 1H), 7.98 (d, 1H), 7.87 (d, 1H), 7.83 (d, 1H), 7.58 (m, 2H), 7.48 (d, 1H), 7.35 (d, 2H), 7.24-7.34 (m, 2H), 6.87 (m, 1H), 2.91 (s, 3H)

^{13}C NMR ($CDCl_3$) δ192.9, 150.1, 136.8, 136.2, 133.3, 132.6, 132.3, 132.2, 131.0, 130.8, 130.6, 130.3, 129.3, 129.0, 128.6, 128.5, 128.4, 127.9, 127.4, 127.3, 127.2, 126.4, 126.2, 123.3, 122.9, 20.9

[M+Na](API/ES) calculated: 369.13 found: 369.13

4-(2-ethynylnaphthalen-1-yl)-1-methylphenanthrene (94). To aldehyde **88** (4.4 g, 12.7 mmol) in MeOH (300 mL) was added K_2CO_3 (3.7 g, 26.7 mmol, 2.1 eq.), then dimethyl (1-diazo-2-oxopropyl)phosphonate (3.2 g, 16.9 mmol, 1.33 eq.) and the resulting mixture was stirred at RT overnight. After NMR-analysis revealed complete conversion, water (1 L), sat. $NaHCO_3$ (500 mL), EtOAc (500 mL) and heptane (500 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (500 mL, 400 mL). The combined organic layers were dried over Na_2SO_4 and concentrated and the residue was filtered over SiO_2 (DCM) to give 3.2 g crude **94** as a yellow foam. This was combined with 700 mg crude **94** from another batch and was purified over 250 mL SiO_2 (toluene) to give **94** (3.1 g, 61%) as a light yellow solid.

^{1}H NMR ($CDCl_3$) δ8.09 (d, 1H), 7.91 (t, 2H), 7.83 (s, 1H), 7.80 (m, 1H), 7.72 (d, 1H), 7.56 (d, 1 H), 7.41-7.47 (m, 2 H), 7.31-7.37 (m, 2H), 7.15-7.28 (m, 2H), 6.89 (1H), 2.88 (s, 3H), 2.73 (s, 1H)

^{13}C NMR ($CDCl_3$) δ147.3, 135.2, 134.5, 133.8, 132.9, 132.2, 131.1, 131.1, 130.0, 129.7, 128.5, 128.2, 127.7, 127.6, 127.1, 127.0, 126.8, 126.1, 125.9, 123.4, 119.183.5, 81.1, 20.9

[M+1](API/ES) calculated: 343.14 found: 343.0

7-methylhexahelicene (95). A solution of alkyne **94** (3.1 g, 9.05 mmol) in toluene (250 mL) was bubbled through with N_2 for 10 min. $PtCl_2$ (241 mg, 0.9 mmol, 10%) was added and the mixture was stirred overnight at 100°C (ext). After NMR-analysis revealed complete conversion, the mixture was evaporated and the residue was filtered over SiO_2 (DCM) to give helicene **95** (3.1 g, quant.) as a light brown solid. Crystallization from HOAc gives helicene **95** as yellow crystals, suitable for X-ray structure determination.

^{1}H NMR ($CDCl_3$) δ8.14 (d, 1H), 7.97 (d, 1H), 7.89-7.95 (m, 2H), 7.78-7.86 (m, 2H), 7.60 (d, 1H), 7.51 (d, 1H), 7.17-7.25 (m, 2H), 6.62-6.69 (m, 2H), 2.92 (s, 3H)

^{13}C NMR ($CDCl_3$) δ133.3, 133.1, 132.1, 131.5, 130.9, 130.2, 130.1, 128.6, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 126.6, 126.5, 125.7, 125.6, 124.8, 124.7, 123.3, 122.3, 20.1

[M+1](ESI) calculated: 343.15 found: 343.15

Hexahelicene-7-carboxylic acid (6). Methylhelicene **95** (1 g, 2.9 mmol) and SeO_2 (810 mg, 7.3 mmol, 2.5 eq.) were heated in Dowtherm A (10 mL) on a preheated plate at 260°C (ext.) while blowing air over the mixture. After 10 minutes all sample has evaporated and after 1.5 h total, NMR analysis showed full conversion of **95**. The mixture is cooled to RT and $CHCl_3$ was added to the residue. The resulting mixture was filtered over Celite and concentrated to give 1.2 g crude acid **6**. The obtained material was purified by column chromatography over 150 mL SiO_2 (toluene : acetone 5 : 1) to give 130 mg of pure acid **6** and 290 mg product containing mix fractions. The mix fractions were purified by column chromatography over 60 mL SiO_2 (toluene : acetone 5 : 1) to give an additional 70 mg of pure acid **6**. The pure fractions were combined to give acid **6** (190 mg, 18%) as a brown solid.

^{1}H NMR ($CDCl_3$) δ9.13 (d, 1H), 8.88 (s, 1H), 8.04-8.11 (m, 2H), 7.93-8.03 (m, 2H), 7.83 (t, 2 H), 7.51 (dd, 2H), 7.18-7.29 (m, 3H), 6.68 (q, 2H)

^{13}C NMR ($CDCl_3$) δ170.3, 132.9, 132.1, 131.6, 131.2, 129.9, 129.5, 129.3, 129.2, 128.9, 128.3, 128.0, 127.8, 127.7, 127.5, 127.4, 127.3, 126.3, 126.2, 125.3, 125.1, 123.1

[M-1](ESI) calculated: 371.12 found: 371.0

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